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## Selective COX-2 inhibitors and renal injury in salt-sensitive hypertension

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**Abstract:** Renal safety of selective COX-2 inhibitors (coxibs) is a matter of ongoing discussion. Therefore, in the present study we examined the effects of two different coxibs, celecoxib and rofecoxib, compared to a traditional NSAID, diclofenac, and placebo in salt-sensitive hypertension. Salt-sensitive (DS) and salt-resistant (DR) Dahl rats were fed with NaCl enriched diet (4% NaCl) for 8 weeks. Diclofenac (DS-diclofenac), rofecoxib (DS-rofecoxib), celecoxib (DS-celecoxib) or placebo were added to chow from week 6 to 8. Immunostaining for monocytes/macrophages (ED1) and cytotoxic T-lymphocytes (CD8) was performed. In addition, renal morphology and proteinuria were assessed. COX-2 protein and mRNA were isolated from renal cortex. Untreated hypertensive animals showed preglomerular and glomerular injury including endothelial activation/proliferation, broadened adventitia, collapsing glomerulopathy, mesangial sclerosis, mesangiolysis, extracapillary proliferation, protein drops and especially high grade of glomerulosclerosis ( $p < 0.05$  vs DR-placebo) and CD8 and ED1 positive cells ( $p < 0.01$  vs DR-placebo) which was improved by celecoxib but not by diclofenac and rofecoxib. Proteinuria was observed in hypertensive animals ( $p < 0.0001$  vs DR-placebo), normalised by celecoxib ( $p = 0.0015$  vs DS-placebo) and increased by rofecoxib ( $p < 0.05$  vs DS-placebo). COX-2 protein and mRNA levels were comparable in all groups. Renal function and morphology improves after celecoxib but not after rofecoxib or diclofenac. This head-to-head comparison demonstrates differential effects of coxibs on renal morphology and function in salt-dependent hypertension

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with mild rise of creatinine levels. The aim of this study is to know the prevalence and significance of hypertension patients nephropathy.

**Patients and Methods:** Descriptive and transversal study with hypertensive patients attended at first time in an Hypertension Unit from 1997 to June 2004. Samples to determine serum creatinine level and urinary protein level were obtained. Other cardiovascular risk factors were detected.

**Results:** 1167 patients were included in the study. Mean age was  $54.29 \pm 14.34$  (40.9% male). Creatinine level over 1.2 mg/dl was found in 240 patients. Mean variable of patients were: male (72.5%;  $p < 0.0001$ ) (OR 5.42 3.96-7.43), age ( $58 \pm 14.4$  vs  $53.32 \pm 14.17$  year old;  $p < 0.0001$ ), uric acid ( $7.1 \pm 1.2$  vs  $5.52 \pm 1.54$  mg%  $p < 0.0001$ ), total cholesterol, LDL cholesterol, triglycerides, smokers and microalbuminuria. All of them have more organ damage: ischemic cardiopathy and cerebral arterial disease (10.4% vs 4.5% ( $p < 0.0001$ ) OR 2.45 (1.46-4.10), and retinopathy.

**Conclusion:** Prevalence of mild renal failure in hypertensive patients is high. These patients also have more organ damage.

Key Words: Hypertension, Prevalence, Renal Failure

### P-340

#### RENAL INSUFFICIENCY IS THE MOST PREVALENT TARGET-ORGAN DISEASE IN PRIMARY CARE-ATTENDED ESSENTIAL HYPERTENSION

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The JNC 7 report included an estimated glomerular filtration rate (eGFR)  $< 60$  ml/min/1.73 m<sup>2</sup> within target-organ diseases. The aim of the present study was to assess the prevalences of target-organ damages in a broad sample of hypertensive patients.

A multicenter, cross-sectional observation of unselected patients with treated essential hypertension attending primary health centers was performed between January and September 2003. Prevalences of target-organ diseases were evaluated. Renal function was estimated by Levey equation. An eGFR  $< 60$  ml/min/1.73 m<sup>2</sup> was considered as renal insufficiency (RI).

Data from 2,517 patients were analyzed, 61.3% female. Mean age was  $69.1 \pm 12$  years. Mean systolic BP was  $139 \pm 16$  mmHg and mean diastolic BP pressure was  $79 \pm 9$  mmHg. Prevalences of target-organ diseases were: RI 36.9%, coronary heart disease (CHD) 12.7%, left ventricular hypertrophy 12.5%, stroke 8.9%, heart failure (HF) 5.6%, and peripheral arterial disease (PAD) 4.4%. RI was the most frequent target-organ disease within men (24.9% vs CHD 15.8%, stroke 11.4%, HF 5.5%, and PAD 7.7%) and women (44.4% vs CHD 10.9%, stroke 7.4%, HF 5.8%, and PAD 2.3%), and within patients aged 40 to 59 years (7.1% vs CHD 5.0%, stroke 3.4%, HF 1.1%, and PAD 0.9%), 60 to 69 years (32.6% vs CHD 10.2%, stroke 5.7%, HF 2.9%, and PAD 3.4%), and 70 or more years (50.9% vs CHD 16.8%, stroke 12.6%, HF 8.5%, and PAD 6.3%). Percentage of patients with RI but without cardiovascular disease or diabetes, mentioned as candidates for secondary prevention, was 19.9%.

Renal disease is simultaneously a major risk factor and a target-organ disease highly prevalent in hypertensive patients followed at the primary care level. RI can be an associated condition more prevalent than classic target-organ diseases especially in the elderly. Adequate screening of renal impairment, as recommended by recent guidelines, must be at the basis of risk stratification and target-organ disease assessment.

Key Words: Essential Hypertension, Kidney Disease, Prevalence

### P-341

#### SELECTIVE COX-2 INHIBITORS AND RENAL INJURY IN SALT-SENSITIVE HYPERTENSION

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Renal safety of selective COX-2 inhibitors (coxibs) is a matter of ongoing discussion. Therefore, in the present study we examined the effects of two different coxibs, celecoxib and rofecoxib, compared to a traditional NSAID, diclofenac, and placebo in salt-sensitive hypertension.

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*Renal function and morphology improves after celecoxib but not after rofecoxib or diclofenac. This head-to-head comparison demonstrates differential effects of coxibs on renal morphology and function in salt-dependent hypertension.*

Key Words: Hypertension, Inflammation, Kidney

### P-342 MP-32

#### DIFFERENTIAL REGULATION OF ACE2 GENE EXPRESSION IN THE HEART AND KIDNEY OF NORMOTENSIVE RATS

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ACE2, a recently described homologue of ACE, catalyses the cleavage of angiotensin II (Ang II) into the vasodilator, natriuretic, and anti-proliferative peptide angiotensin-(1-7) [Ang-(1-7)]. The role of Ang-(1-7) as a cardio-renal protective hormone was further illuminated by our demonstration that blockade of type 1 Ang II receptors (AT<sub>1</sub>-R) in Lewis rats caused a 3-fold upregulation of cardiac ACE2 mRNA paralleled with increased plasma Ang-(1-7) levels and reversal of heart failure post-myocardial infarction (Ishiyama et al. *Hypertension* 43: 970-976, 2004). The demonstration that blockade of the AT<sub>1</sub>-R modulates cardiac ACE2 gene expression raised the question whether the same effect may be produced in the kidney where ACE2 gene expression is high and Ang-(1-7) is critically involved in the control of renal function. Thirty-six male 10 wk old normotensive Lewis rats received vehicle, lisinopril, losartan, or both drugs in combination in the drinking water for 12 days (10 mg/kg/day for each of the agents). Combination therapy (lisinopril + losartan) produced the largest decrease in tail-cuff systolic blood pressure ( $-41$  mm Hg)